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Antidiabetic Therapy in Type 2 Diabetic Patients on Hemodialysis

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1. Introduction

Diabetic nephropathy is the most common cause for end-stage renal disease (ESRD). Chronic renal failure is associated with miscellaneous alterations in carbohydrate and insulin metabolism. Moreover, several specific therapies employed in renal insufficiency also influence pharmacological therapy of diabetes in uraemic patients. In patients with altered renal function, therapeutic possibilities are limited due to the accumulation of some oral agents and/or their metabolites at the reduced glomerular filtration rate (GFR). The connection between kidney and insulin metabolism is well known for many years (Horton et al, 1968). For insulin metabolism the kidneys are one of its target organs. Chronic renal failure is associated to multiple alterations in the carbohydrate and insulin metabolism that should be taken into account when treating diabetic patients with altered renal function (DeFronzo et al, 1973). Specific therapeutic needs (oral agents or insulin) will be determined based on the degree of insulin resistance or insulin deficiency of patients with renal insufficiency (Rabkin et al, 1984). A good metabolic control is not only important in the early phase of diabetic nephropathy but also in diabetic patients with ESRD. It was shown in several studies, that metabolic control under antidiabetic therapy is a predictor for prognosis of patients with renal replacement therapy (Morokia et al, 2001). A good glycemic control can reduce the progression of atherosclerosis (Oomichi et al, 2006) and improve the survival in patients treated with hemodialysis (Kovesdy et al, 2008). Though, in a recent study it was suggested that aggressive glycemic control cannot be routinely recommended for all diabetic hemodialysis patients on the basis of reducing mortality risk (Williams et al, 2010). The majority of uraemic type 2-diabetic patients need insulin, however, a smaller part of these diabetic patients can also be treated with oral antidiabetic agents.

The problem of the topic of this study is the fact, that there are only few data in the literature concerning antidiabetic therapy in type 2 diabetic patients with ESRD (Biesenbach et al, 2010). This paper offers a review of the relevant findings related to insulin therapy in diabetic patients with ESRD. Additionally, we review the relevant aspects related to oral antidiabetic therapy in diabetic patients with impaired renal function.

2. Insulin metabolism and insulin therapy

The insulin metabolism is changed in uraemic patients. In insulin-treated diabetic patients suffering from renal insufficiency the insulin requirement is reduced in renal insufficiency.

Additionally, hemodialysis influences insulin metabolism and the glycemic control under antidiabetic therapy. In this overview the insulin metabolism in uremic patients and the insulin therapy as well as oral antidiabetic therapy will be discussed.

2.1 Insulin metabolism in uremic patients

Insulin is a polypeptide hormone (51-amino acids), the molecular weight of approximately 6000 Da, The Half-life ($t_{1/2}$) of insulin is short (3–5 min). Under fasting conditions the insulin secretion rate is 0.5–1 unit/h. After meal insulin secretion shows a 3–10 fold increase (Polonsky et al 1986). In healthy subjects insulin is secreted into the portal system, insulin passes through the liver, where about 75% is metabolized, with the remaining 25% metabolized by the kidneys. About 60% of the insulin in the arterial bed is filtered by the glomerulus, and 40% is actively secreted into the nephric tubules. Most of the insulin in the tubules is metabolized into amino acids, and only 1% of insulin is secreted intact (Mak et al, 1992). As parameter for endogenous insulin secretion C-peptide can be used. Unlike insulin, C-peptide is not metabolized during its first pass through the liver and, approximately 70% of its plasma clearance is performed in the kidney (Block et al, 1972)

For diabetic patients receiving exogenous insulin, renal metabolism plays a more significant role since there is no first-pass metabolism in the liver. As renal function starts to decline, insulin clearance does not change appreciably, due to compensatory peritubular insulin uptake. But once the GFR drops below 20–30 mL/min, the kidneys clear significantly less insulin, an effect causally determined by a decrease in the hepatic metabolism of insulin that occurs in uremia. Despite an increase in insulin resistance caused by renal failure, the net effect is a reduced requirement for exogenous insulin in ESRD as the result of periodic improvement in uremia, acidosis, and phosphate handling (Shrishrimal et al, 2009).

Thus, in the presence of impaired renal function, the type 1 as well as type 2 diabetic patients require less insulin, mainly due to prolonged insulin clearance (Biesenbach et al, 2003). For these reasons the American College of Physicians recommends to decrease insulin doses by 25% of initial insulin dose when GFR is 50–10 mL/min and by 50% when GFR is less than 10 mL/min (Aronoff et al 1999). Other factors that contribute to decreasing exogenous insulin requirements in CRF diabetic patients are the reduction of renal gluconeogenesis, uraemia-induced anorexia and weight loss (Charpentier, et al, 2000)

In ESRD, both uremia and dialysis can complicate glycemic control by affecting the secretion, clearance, and peripheral tissue sensitivity of insulin. Several factors, including uremic toxins, may increase insulin resistance in ESRD, leading to a blunted ability to suppress hepatic gluconeogenesis and regulate peripheral glucose utilization. In type 2 diabetes without kidney disease, insulin resistance leads to increased insulin secretion. This does not occur in ESRD because of concomitant metabolic acidosis and vitamin D deficiency (Shrishrimal et al, 2009). Impairment of renal function is associated with insulin resistance, this resistance can be improved by start of hemodialysis (Rabkin et al, 1984) Hemodialysis alters insulin secretion, insulin clearance, and resistance.

In an own study the mean decrease of required insulin dose dependent on time was slightly lower in type 1 diabetes with 2.8 IU/year versus 3.8 IU/year in type 2 diabetes (NS). The decline in insulin requirement increased significantly when GFR decreased below 30 mL/min.

The reduction of insulin requirement at the beginning of decline of renal function may be explained by study associated improvement of glycemic control.

We also measured C-peptide at the beginning and the end of renal function impairment, the mean difference was not significant with 2.2 versus 2.7 ng /ml. Thus, we assumed that residual insulin secretion has no significant impact on the reduction in insulin requirement dependent on GFR. Insulin therapy in patients on hemodialysis is associated with hyperinsulinemia and a higher incidence of hypoglycaemia compared to patients without dialysis (Loipl et al, 2005). In rare cases insulin substitution can be stopped in type 2 diabetic patients with already low insulin requirement already in the pre-dialysis phase.

2.2 Practical managing of insulin therapy in patients on hemodialysis

Most type 2 diabetic patients with ESRD need insulin therapy. In patients with renal insufficiency it may be considered that intensive insulin therapy can help to improve glycaemic control more than conservative insulin therapy. There is lack of relevant pharmacokinetic studies for the various types of insulin in patients with different degrees of renal insufficiency (Snyder & Berns, 2004): Due to the absence of comparative studies there are no therapeutic guidelines that define insulin adjustments based on GFR (Bilous et al, 2004). In hemodialysis patients with type 2 diabetes insulin requirements are usually reduced in probable relationship with an improvement in insulin resistance associated with the dialytic procedure (Schmidt et al, 1984). Additionally, a reduced insulin clearance may contribute to the decrease in requirement of insulin. On the basis of evidence, it can be recommended a basis-bolus insulin regime with the long-acting insulin glargine (Lantus®) or detemir (Levemir®) for basal requirements, along with a rapid-acting insulin analogue such as lispro (Humalog®), insulin aspart (NovoLog®, Novorapid®) or insulin glulisine (Apidra®) before meals. Duration of action of insulin glargine is significantly longer than that of human NPH insulin (IProtaphan®, Basal®, Humulin®) with a less pronounced peak of action (Iglesias et al, 2008). In the literature the T_{max} averages were 8.6 hours for insulin glargine compared to 5.4 hours for NPH insulin. Lower FPG (fasting plasma glucose) levels with fewer episodes of hypoglycemia are achieved with insulin glargine compared to NPH insulin. Insulin glargine is metabolized at the carboxyl terminal of the B chain to two metabolites) with activity similar to that of human insulin (Ersoy et al, 2006). Few studies were published comparing analogue insulin and regular insulin (Aisenpreis et al, 1999). Both, short acting as well as long acting insulin analogues have advantages in comparison to regular insulin. During the last years in most centers the NPH insulin was replaced by the long acting insulin analogues glargine or detemir. Meanwhile, several studies have described the use of insulin analogues in ESRD (O'Mara et al, 2010). Nevertheless, clinical efficacy and safety profile of insulin analogues are not clearly defined in chronic renal failure. Since of potentially carcinogenic and proliferative effects have not yet been disproved. Most studies with analogues to date have excluded diabetic patients with advanced diabetic complications. Therefore, there is little information regarding the use of these analogues in renal insufficiency. The main advantage of the short-acting insulin analogue is the shorter absorption, the most important advantage of the long-acting insulin analogues is the lower risk of hypoglycemia, thus improving glycemic control and improving quality of life (Jehle et al, 1999). In insulin-treated type 2 diabetic patients with low insulin requirement (<20 IU/day) a conventional insulin regime may such also be used, such as daily 1-2 injections of a long acting insulin or a pre-mixed insulin-combination (NPH-insulin and normal insulin or short-acting insulin analogues). When GFR decreases to 10-50 mL/min, the total dose of both, regular insulin or insulin analogue should be reduced by 25%. In patients with ESRD, the insulin dose should be reduced by 50%.

However, there are great interindividual differences in the decrease of insulin requirement (Biesenbach et al, 2003)

The insulin requirement in hemodialysis patients in dialysis is very different. In an own study we investigated the insulin requirement during the first dialysis year in insulin-treated type 2 diabetic patients dependent on rest diuresis. Patients were divided into two groups according to their diuresis. Group 1, of patients with preserved near-normal urine production (>1 l/day) during the first dialysis year ($n = 12$), and group 2, of patients with significant reduction of urine excretion (<0.5 l/day) within 3 months after start of dialysis ($n = 12$). All patients were dialysed three times per week (total dialysis time 12 h weekly). The HbA1c- were similar in both groups and did not significantly change during the first year. Insulin requirement in the patients with normal diuresis decreased from 24 IU/day at the start of dialysis to 14 ± 8 IU/day 1 year later (41% reduction, $P < 0.05$). In the group with reduced diuresis, the required insulin dose remained the same with 28 ± 12 and 26 ± 8 IU/day, respectively (7% reduction). We concluded that in insulin-treated diabetic patients the insulin requirement can be different due to differences in the residual renal function. During the first year hemodialysis the insulin requirement can further drop in patients with decreasing diuresis (Biesenbach et al, 2008). However, the evidence of this study limited due to the small patient groups.

The targets of therapy in patients with ESRD are similar as in subjects with normal GFR; The targets are a hemoglobin A1c value between 6% and 7%, a fasting blood glucose level less than 140 mg/dL, and a postprandial glucose level less than 200 mg/dL. The individual targets of therapy may be changed depending on the higher risk for hypoglycemia in patients on hemodialysis (Uzu et al, 2008)

3. Oral antidiabetic drug therapy

Type 2 diabetic patients with ESRD need in the majority insulin therapy, however, some patients are treated by oral anti-diabetic drugs or diet alone. In type 2 diabetes and terminal renal failure several drugs can be used. Nevertheless, Most oral antidiabetic drugs are not recommended under hemodialysis therapy.

3.1 Old oral antidiabetic drugs

Three “old” agents have been approved for patients with renal insufficiency.

Sulfonylurea (SU) drugs can be used in diabetic patients with ESRD (Charpentier et al, 2009): Glipizide (Glucenorm®) can be used with normal dose, gliclazide (Diamicon®) and glimepiride (Amaryl®) in reduced dose (50%). Under hemodialysis SU drugs should rather be avoided due to the higher risk of hypoglycaemia. Glibenclamide (Euglucon®) is absolutely contraindicated in renal insufficiency due to severe hypoglycemia (Krepinsky et al, 2000).

Alpha-glucosidase inhibitors

Both, the alpha-glucosidase inhibitor acarbose (Glucobay®) and especially miglitol (Diastabol®) are contraindicated in ESRD (Yale 2005)

Biguanides

Metformin (Glucophage®, Diabetex®, Metformin®) is a biguanide that reduces hepatic gluconeogenesis and glucose output. It is contraindicated in patients with renal disease

(s-creatinine >1.1 mg/dl in women and >1.4 mg/dl in men) and also in congestive heart failure due to the risks of lactic acidosis. However, in some studies the authors suggested that the use of metformin in patients who are over the age of 80 years, have congestive heart failure or have renal insufficiency leads to a benefit that far outweighs the potential harm. (McCormack et al, 2005)

3.2 New antidiabetic drugs

In this group three “new” agents are included: insulin secretizers (glinide), insulin sensitizers (glitazone) and the new group of GLP 1 agonists and DPP inhibitors (gliptine) (Mohideen et al, 2005)

Meglitinides

There are two glinides, repaglinide (Novonorm®; Prandin®) and nateglinide (Starlix®) are insulin secretagogues, both can be used in renal failure, but not recommended for patients on hemodialysis (Nagai et al, 2003)

Thiazolidinedione (glitazone)

Pioglitazone (Actos®) do not need dosing adjustment. Main adverse effect of this agent is edema, therefore it is contraindicated in heart failure, especially when combined with insulin therapy. Since the end of 2010 only pioglitazone is available. Rosiglitazone (Avandia®) was removed due to an increased cardiovascular risk (Thompson-Culkin et al, 2002)

Incretin (GLP-1 Analogues and Gliptins)

Glucagon-like peptide-1 (GLP-1) stimulates glucose-dependent insulin release from pancreatic beta cells and inhibits inappropriate postprandial glucagon release. It also slows gastric emptying and reduces food intake. Dipeptidyl peptidase IV (DPP-IV) is an active ubiquitous enzyme that deactivates a variety of bioactive peptides, including GLP-1. **Exenatide** (Byetta®) is a naturally occurring GLP-1 analogue that is resistant to degradation by DPP-IV and has a longer half-life. Given subcutaneously, no dose adjustment is required if the glomerular filtration rate (GFR) is greater than 30 mL/min. The drug's label has been updated to note that the drug should not be used in patients with severe renal impairment; Exenatide is absolutely contraindicated in patients on hemodialysis (Kuehn, 2011). **Sitagliptin** (Januvia®) was the first oral DPP-IV inhibitor, the usual dose of sitagliptin is 100 mg once daily, with reduction to 50 mg for patients with a GFR of 30 to 50 mL/min, and 25 mg for patients with a GFR < 30 mL/min (Bergman et al, 2007). Further vildagliptin (Galvus®), normal dose 2x50 mg daily, a dose reduction is recommended for patients with moderate to severe renal impairment (Thuren et al, 2008).

4. Fluctuation of blood glucose and monitoring of glycemic control

Several factors can negatively influence glycaemic control in diabetic patients. These include poor food intake, insufficient exercise, uraemia-induced anorexia, insulin metabolism disorders, especially insulin resistance and reduced insulin clearance, and inadequate drug therapy. In diabetic patients with ESRD additional factors can cause blood glucose (BG) fluctuations.

4.1 Fluctuations of blood glucose under hemodialysis

High fluctuations of blood glucose (BG) are characteristically in insulin-dependent diabetic patients on hemodialysis. Several factors contribute to these wide fluctuations in BG-levels and increase the risk of hypoglycemic events. Hemodialysis may cause hypoglycemia due to a decrease of plasma glucose and immunoreactive insulin. Patients undergoing hemodialysis may become hypoglycemic and not be aware of it. There is no hormonal imbalance causing the hypoglycemia and the hormonal response to the hypoglycemia is blunted. Patients with an initial plasma glucose of 5.5 mmol/l (100 mg/dl) or less who are hemodialyzed and who do not eat during dialysis may be particularly at risk, especially if they are on insulin or taking glucose-lowering medication. These should be dialyzed with a dialysis fluid containing at least 5.5 mmol/l (100 mg/dl) glucose. (Jackson et al, 2000). In patients with poor metabolic control, hyperglycemia appears immediately post-hemodialysis; this was attributed partly to the hemodialysis-induced decrease in the plasma immunoreactive insulin levels. In summary, hemodialysis causes hypoglycemia during dialysis and hyperglycemia post-dialysis by absolute or relative plasma immunoreactive insulin deficiency (Shrishrimal, 2009). The dextrose concentration in the dialysate can affect glucose control in both ways. Dialysates with lower dextrose concentrations may be associated with hypoglycemia, dialysates with higher dextrose can lead to hyperglycemia. Most dialysis centers are using dialysate with 100mg/dl glucose concentration. Furthermore, there it was reported that hypoglycemia is usual at the day following hemodialysis, the authors recommended a reduction of the basal insulin dose at these days. Recent study has demonstrated a significant 25% reduction in basal insulin requirements the day after dialysis compared to the day before. No significant change in bolus insulin was observed, and overall the reduction of total insulin requirements was -15% (Sobngwi et al, 2010).

Insulin in peritoneal dialysis

The fluctuations of blood glucose, hyperinsulinemia and the rare formation of insulin antibodies under subcutaneous insulin (sc) injection can be prevented by peritoneal dialysis (PD). Investigations of insulin in patients treated with PD indicate that the intraperitoneal (ip) administration of insulin leads to more even glucose levels, but that when dialysis fluids with glucose concentrations higher than 13.6 g/L are used, the absorption of glucose from the abdominal cavity is greater in PD with ip insulin treatment than it is with sc administration (Quellhorst, 2002).

The raised glucose absorption from the abdominal cavity in ip insulin administration must be regarded as a disadvantage. Investigations of insulin in PD showed, that after a dwell time of 30 min, the absorption of insulin from the abdominal cavity in the patients with diabetes was much higher than in the patients without diabetes. In several studies the authors compared both routes of insulin administration. they observed a better fall of HbA1c after switching from sc to ip administration (Grodstein et al, 1981).

4.2 Monitoring of glycemic control

It is well known that hemoglobin A(1c) is no exact parameter for glycemic control in uremic diabetic patients (Joy et al, 2002). Especially, the hemoglobin A(1c) level can be falsely high in ESRD, but it is still a reasonable measure of glycemic control in this population. The cause of the falsely elevated level in diabetic patients with ESRD is the elevated blood urea nitrogen, which causes formation of carbamylated hemoglobin, which is indistinguishable from glycosylated hemoglobin. Other factors such as the shorter red life span of red blood cells,

iron deficiency, recent transfusion, and use of erythropoietin-stimulating agents may also cause underestimation of glucose control. In a recent study it was reported that glycated albumin is a better glycemic indicator than glycated hemoglobin values in hemodialysis patients with diabetes (Inaba, et al, 2007) However, in the clinical practise glycated hemoglobin was not replaced by glycated albumin or fructosamine

5. Metabolic control and vascular diseases dependent on antidiabetic therapy

There are only few data in the literature concerning metabolic control under different - antidiabetic therapy. In a recent study we investigated metabolic control and vascular diseases in 64 type 2 diabetic patients under chronic hemodialysis therapy. 42 patients (65%) received insulin therapy (n=42) versus 12 patients oral antidiabetic drug therapy (19%). 10 patients were treated with diet alone (16%). Observation period was the first year of hemodialysis (Biesenbach et al, 2010). The baseline data are summarized in table 1, The

	Oral SU	Insulin	Diet alone
Number (n)	12	42	10
Age (years)	63 $\pm$ 16	62 $\pm$ 11	62 $\pm$ 11
Female (n/ %)	6 (50%)	24 (57%)	5 (50%)
Body weight	78 $\pm$ 21	79 $\pm$ 18	76 $\pm$ 16
Diabetes duration (years)	13 $\pm$ 4	16 $\pm$ 5**	6 $\pm$ 3**
C-Peptide (ng/ ml)	2.2 $\pm$ 1.1	1.8 $\pm$ 0.9*	2.4 $\pm$ 1.1*
Hypertension (n)	10 (87%)	38 (90%)	8 (80%)
Antihypertensive drugs (n/ %)	2,3 (0- 4)	2,1 (0-4)	2.0 (0-3)
Statine (n/ %)	4 (33%)	14 (33%)	4 (40%)
Smoker (n/ %)	4 (33%)	12 (28%)	3 (33%)

*p<0.05, **p<0.01

Table 1. Baseline data before the start of hemodialysis in patients with sulfonylurea (SU) or insulin therapy and/or diet alone

5.1 Metabolic control dependent on antidiabetic therapy

HbA1c values were similar in each groups at the start of HD as well as after one year. Hypoglycemia occurred more frequently in the insulin-treated patients, however the difference was not significant. The triglycerides were significantly lower in the insulin-treated patients (138 $\pm$ 28 versus 176 $\pm$ 46 mg/dl, (p<0.05). The body weight was similar in each group, during 12 months a slightly weight loss (1-2%) could be observed in the group with oral antidiabetic and insulin therapy. The metabolic control in the three patient groups is presented in table 2 and 3 as well as table 4.

The C-peptide at the start of HD was lower in the insulin treated patients with 1.8 $\pm$ 0.9 ng/ml versus 2.2 $\pm$ 1.1 and 2.4 $\pm$ 1.1 ng/ml in the other groups (p<0.05). During the first 12 months after the start of hemodialysis in the patient group with SU therapy two patients became insulin dependent, on the other group insulin therapy could be stopped in two cases, a reduction of insulin dose was necessary in 2 patients (48%).

	At start of HD	after 12 months	changes
HbA1c (%)	7.6 $\pm$ 1.3	7.7 $\pm$ 1.2	+ 1%
Hypo (n/ patient/ month)	0.6	0.9	+50%
Body weight (kg)	78 $\pm$ 21	76 $\pm$ 18	-2%
Cholesterol (mg/ dl)	168 $\pm$ 44	156 $\pm$ 33	-7%
Triglycerides (mg/ dl)	188 $\pm$ 48	176 $\pm$ 46	-6%
SU gliclazid/ glimerpirid (n)	6/6	4/4	
SU changed to insulin (n)	0	2	16%
SU changed to diet alone (n)	0	2	16%

Table 2. Metabolic control at the start and after 12 months hemodialysis in patients with sulfonylurea (SU) as oral antidiabetic therapy.

	At start of HD	after 1 year	changes (%)
HbA1c (%)	7.9 $\pm$ 1.1	7.7 $\pm$ 0.8	-2%
Hypoglycemia (n/ patient/ month)	0.6	1.1	+83%
Body weight (kg)	79 $\pm$ 18	78 $\pm$ 17	-1%
Cholesterol (mg/ dl)	154 $\pm$ 42	144 $\pm$ 36	-6%
Triglycerides (mg/ dl)	144 $\pm$ 38	138 $\pm$ 28	-4%
Insulin dose (U/ patient/ day)	28 $\pm$ 6*	22 $\pm$ 5*	-21%
Insulin changed to SU (n)	0	1	8%
Insulin changed to diet alone (n)	0	1	8%

*p<0.05

Table 3. Metabolic control at the start and after 12 months hemodialysis in patients with insulin therapy.

	At the start of HD	after 1 year	changes (%)
HbA1c (%)	7.4 $\pm$ 0.8	7.1 $\pm$ 0.6	-4%
Hypoglycemia (n/ patient/ month)	0,4	0,6	+50%
Body weight (kg)	76 $\pm$ 16	76 $\pm$ 12	0%
Cholesterol (mg/ dl)	182 $\pm$ 38	178 $\pm$ 33	-3%
Triglycerides (mg/ dl)	164 $\pm$ 32	160 $\pm$ 33	-3%
Diet alone changed to insulin	0	0	0%
Diet alone changed to antidiabetic drug	0	1	10%

Table 4. Metabolic control at the start and after12 months hemodialysis in patients with diabetes diet alone.

5.2 The prevalence of vascular diseases depended on antidiabetic therapy

The prevalence of vascular diseases was only slightly higher in the insulin-treated patients (NS). The prevalence of coronary artery disease was 45% in the CAD group versus 33% and 30% in the other two groups. This may be caused by a significantly higher diabetes duration. The prevalences are also shown in figure 1 The similar prevalence of macroangiopathy at the start of dialysis is not surprisingly, in each patient group the vascular risk factors were similar. The renal disease in type 2 diabetic patients at ESRD is in the majority a diabetic nephropathy (70-80%) The other diabetic patients mostly suffer from a vascular nephropathy (15-25%). It may be assumed that patients with vascular disease need more often only diet alone. In an earlier study we reported, that during the last 3 years before start of dialysis, progression of diabetic and vascular nephropathy with fall in GFR, were similar, and the prevalence of vascular diseases too (Biesenbach et al, 2006). Surprisingly, there is no relevant study in the literature concerning differences in the antidiabetic therapy between patients with diabetic and vascular nephropathy. In a recent study comparing the outcome of patients with diabetic and vascular nephropathy, we reported that insulin was used in 67% of the patients with diabetic nephropathy versus in only 25% of those with vascular nephropathy (Stieglmayr et al, 2010)

Fig. 1. Prevalence of cerebrovascular disease (CVD), coronary artery disease (CAD) and peripheral artery disease (PAD) dependent on anti-diabetic therapy with diet alone, Insulin or sulfonylurea (SU) drug.

6. Conclusions

Antidiabetic therapy in patients with ESRD can be difficult, both, the administration of oral antidiabetic drugs as well as the insulin injection. To obtain a good glycemic control in chronic renal insufficiency multiple factors intrinsic to diabetes, renal insufficiency and therapy has to be taken into account. Insulin resistance and hyperinsulinaemia can impair the capacity of antidiabetic therapy. The requirement of insulin decreases in renal insufficiency due to reduced insulin clearance. Intensive insulin therapy is the adequate method for improving glycaemic control in ESRD. The most common side effect of insulin is hypoglycemia. In the few studies reported until now, the use of insulin analogues in uremic

patients has been associated with potential advantages and benefits with regard to glycaemic control, yet without any significant elevation in hypoglycaemic event frequency. Intensified insulin therapy, the basis bolus regime, should be preferred, in type 2 diabetes with low insulin requirement a conventional insulin therapy can also be used.

7. Summary – important factors of antidiabetic therapy in ESRD

- Wide fluctuations in blood glucose levels are characteristically in diabetic patients on hemodialysis
- Most of the diabetic patients with ESRD need insulin- therapy, only a small group of these patients can be treated with oral antidiabetic drugs
- Several oral antidiabetic drugs like glinide, glitazone and gliptine as well as some SU agents can be used in patients with renal insufficiency, in patients on hemodialysis in most cases a drug dose reduction by 50% is necessary in most cases.
- Most diabetes drugs are excreted at least in part by the kidney, so that patients in ESRD are at greater risk of hypoglycemia
- Impairment of renal function is associated with reduced insulin clearance , therefore, insulin doses should be lowered in patients with low GFR.
- In patients with insulin therapy hypoglycaemia occurs more frequently during dialysis and hyperglycemia after dialysis due to insulin deficiency-
- The hemoglobin A1c level can be falsely high in ESRD, but there is no alternative, it is still a reasonable measure of glycemic control
- The prevalence of vascular diseases is not significantly different in the the patients with insulin versus oral antidiabetic therapy

8. References

- Aisenpreis U, Pfu tzner A, Giehl M, Keller F, Jehle PM. *Pharmacokinetics and pharmacodynamics of insulin lispro compared with regular insulin in haemodialysis patients with diabetes mellitus*. Nephrol Dial Transplant 14 (Suppl. 4): 5–6, 1999
- Aronoff GR, Berns JS, Brier ME et al. eds. *Drug Prescribing in Renal Failure. Dosing Guideline for Adults*, 4th edn. Philadelphia: American College of Physicians, 1999.
- Bergman AJ, Cote J, Yi B et al. *Effect of renal insufficiency on the pharmacokinetics of sitagliptin, a dipeptidyl peptidase-inhibitor* Diabetes Care 30: 1862-1864, 2007
- Biesenbach G, Bodlaj G, Ebner S, Biesenbach P, Pieringer H *Metabolic control and vascular diseases under oral antidiabetic drug versus insulin therapy and/or diet alone during the first year of hemodialysis in type 2 diabetic patients with ESRD* Int Urol Nephrol 20: 642-645 2010.
- Biesenbach G, Raml A, Schmekal B, Eichbauer-Sturm G. *Decreased insulin requirement in relation to GFR in nephropathic Type 1 and insulin-treated Type 2 diabetic patients*. Diabet Med. 8:642-45, 2003
- Biesenbach G, Bodlaj G, Pieringer H, SedlakM. *Influence of residual diuresis on insulin requirement in insulin-treated type 2 diabetic patients during the first year of hemodialysis*. Nephrol Dial Transplant. 23(1):422-423, 2008
- Biesenbach G, Schmekal B, Pieringer H, Janko O *Rate of decline of GFR and progression of vascular disease in type 2 diabetic patients with diabetic or vascular nephropathy during the*

- last three years before starting dialysis therapy.* Kidney Blood Press Res. 29(5):267-672, 2006
- Block M, Mako M, Steiner D, Rubenstein A. *Circulating -peptide immunoreactivity studies in normal and diabetic patients.* Diabetes 21: 1013-1024, 1972
- Bridget M. Kuehn. *Exenatide and kidney function.* YAMA 302: 2466, 2010
- Charpentier G, Riveline JP, Varroud-Vial M. *Management of drugs affecting blood glucose in diabetic patients with renal failure.* Diabetes Metab 26: 73-85. 2002
- DeFronzo RA, Andres R, Edgar P, Walker WG. *Carbohydrate metabolism in uremia. A review.* Medicine 52: 469-481. 1973
- Ersoy A, Ersoy C, Altinay T. *Insulin analogue usage in a haemodysis patient with type 2 diabetes mellitus.* Nephrol Dial Transplant. 21(2):553-554, 2006
- Grodstein GP, Blumenkrantz MJ, Kopple JD; Moran JK, Coburn JW: *Glucose absorption during continuous ambulatory peritoneal dialysis.* Kidney Int 19: 564, 1981
- Horton ES, Johnson C, Lebovitz HE. *Carbohydrate metabolism in uremia.* Ann Intern Med 1968; 68: 63-74. 1968
- Jehle PM, Aisenpreis U, Bundschu D, Keller F. *Advantages of insulin lispro (short-acting) in terminal kidney failure.* Fortschr Med 20: 41-42. 1999
- Iglesias P and Diez J *Insulin therapy in renal disease* Diabetes, Obesity and Metabolism, 10, 811-823, 2006
- Inaba M, Okuno S, Kumeda Y, et al. (2007) Osaka CKD Expert Research Group. *Glycated albumin is a better glycemic indicator than glycated hemoglobin values in hemodialysis patients with diabetes: effect of anemia and erythropoietin injection.* J Am Soc Nephrol 18:896- 903, 2007
- Jackson MA, Holland MR, Nicholas J, Lodwick R, Forster D, Macdonald IA (2000). *Hemodialysis-induced hypoglycemia in diabetic Patients* Clin Nephrol. 54:30-34, 2000
- Joy MS, Cefali WT, Hogan SL, Nachman PH *Long-term glycemic control measurements in diabetic patients receiving hemodialysis.* Am J Kidney Dis 2002; 39:297-307, 2002
- Kovesdy Kovesdy C, Sharma K, Kalantar-Zadeh. *Glycemic control in diabetic CKD patients: where do we stand?* Am J Kidney Dis 52: 6766-777, 2008
- Jackson MA, Holland MR, Nicholas J, Lodwick R, Forster D, Macdonald IA (2000). *Hemodialysis-induced hypoglycemia in diabetic Patients* Clin Nephrol. 54:30-34, 2000
- Loipl J, Schmekal B, Biesenbach G *Long-term impact of chronic hemodialysis on glycemic control and serum lipids in insulin-treated type 2-diabetic patients.* Ren Fail. 27(3):305-308, 2005
- Mak RH, DeFronzo RA *Glucose and insulin metabolism in uremia.* Nephron 61:377-382, 2002
- McCormack , Johns H, Hildesdey H *Metformin's contraindications should be contraindicated* Canadian Med Ass J 173: 1503, 2005
- Mohadee P, Bornemann M, Sugihara J, G, Arakaki R *The metabolic effects of triglitazone in patients with diabetes and end stage renal disease.* Endokrine 38:181-186, 2005
- Morioka T, Emoto M, Tabata T et al *Glycemic control is a predictor for survival of diabetic patients on hemodialysis.* Am J Kidney Dis 24: 909-913, 2001
- Nagat T, Imamura M, Lizuka K, Mori M. *Hypoglycemia due to nateglinide administration in diabetic patients with chronic renal failure.* Diabetes Res Clin Pract 59:191-194, 2003
- O'Mara NB. *Agents for the treatment of diabetes mellitus.* Semin Dial. 23:475-479, 2010
- Oomichi T, Emoto M, Tabata T et al *Impact of glycemic control on survival of diabetic patients on chronic regular hemodialysis.* Diabetes Care 29: 1496-1500, 2006

- Polonsky KS, Licinio-Paixao J, Given BD et al. Use of biosynthetic human C-peptide in the measurement of insulin secretion rates in normal volunteers and type I diabetic patients. *J Clin Invest* 77: 98-105. 1986
- Quellhorst. *Insulin therapy during peritoneal dialysis: pros and cons of various forms of administration.* . *J Am Soc Nephrol*. 13 Suppl 1:S92-6. 2002
- Rabkin R, Ryann MP, Duckwords WC. *The renal metabolism of insulin.* *Diabetologia* 27; 351-357, 1984
- Shrishrimal, P Hart, F Michota *Managing diabetes in hemodialysis patients: Observations and recommendations* *Cleveland Clinic Journal of Medicine* . 76 11; 649-655, 2009
- Schmidtz O, Alberti KG, Orskov H. *Insulin resistance in uraemic insulin-dependent diabetics. Effect of dialysis therapy as assessed by the artificial endocrine pancreas.* *Acta Endocrinol* 105: 371-378, 1984
- Snyder RW, Berns JS *Use of insulin and oral hypoglycemic medications in patients with diabetes and advanced kidney.* *Semin Dial* 7:365-370, 2004
- Stieglmayr S, Khayyat AH, Bodlaj G, Pieringer H, Biesenbach G. *Comparable outcomes in type 2 diabetic patients with diabetic or vascular nephropathy treated by hemodialysis.* *Nephron Clin Pract* 114 (2) 104-107, 2010
- Thompson-Culkin K, Zussman B, Miller AK Freed MI et al *Pharmacokinetics of rosiglitazone in patients with end-stage renal disease.* *J Int Med Res* 30: 391-399, 2002
- Uzu T, Hatta T, Deji N, Izumiya T et al. *Target for glycemic control in type 2 diabetic patients on hemodialysis: effects of anemia and erythropoietin injection on HbA(1c).* *Ther Apher Dial* 13: 89-94, 2009
- Williams ME *Insulin Management of a Diabetic Patient on Hemodialysis* *Semin Dialysis* 5(1); 69-73, 2007
- Yale J-F *Oral Antihyperglycemic Agents and Renal Disease: New agents, New Concepts* *J Am Soc Nephrol* 16: S7-S10, 2005

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This book provides an overview of special cases in hemodialysis patients. Authors have contributed their most interesting findings in dealing with patients suffering of other diseases simultaneously, such as diabetes, cardiovascular disease and other health problems. Each chapter has been thoroughly revised and updated so the readers are acquainted with the latest data and observations in these complex cases, where several aspects are to be considered. The book is comprehensive and not limited to a partial discussion of hemodialysis. To accomplish this we are pleased to have been able to summarize state of the art knowledge in each chapter of the book.

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